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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,627	06/19/2006	Heinz Von Der Kammer	37998-237368	8551

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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/596,627	VON DER KAMMER ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,12,25 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,12,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10, 13-24, 27 and 28 have been canceled. Claims 11, 12, 25 and 26 remain pending.

Applicant's arguments filed 12-29-08 have been fully considered but they are not persuasive. When referring to the specification originally filed for support for amendments or in arguments, please refer to page number and paragraph and line number as necessary.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

The amendments to the specification adding SEQ ID NOs has been entered.

Claim Rejections - 35 USC § 112

New Matter

Claims 11, 12, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The concept of screening for compounds that decrease neurodegenerative disease in claim 11 as amended is new matter. Paragraph 9 contemplates modulators that decrease the biological activity of a translation product (pg 3, col. 2, ¾ of the way down). The concept of screening for compounds that decrease neurodegenerative

disease now claimed is not readily apparent from the teachings in the specification originally filed.

The broader concept of using any genetically altered Drosophila having symptoms of neurodegenerative disease to screen modulators of HIF3a as in claim 11 as amended is new matter. The specification does not contemplate administering modulators of HIF3a to any genetically altered Drosophila having symptoms of neurodegenerative disease as broadly claimed.

Enablement

Claims 11, 12, 25 and 26 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed toward a method of screening for a compound that decreases neurodegenerative diseases, wherein the compound is a modulator of i) a gene coding for HIF3a, ii) a transcription product of a gene coding for HIF3a, iii) a translation product of a gene coding for HIF3a, and iv) a fragment, derivate or variant of i), ii) or iii).

The claims are directed toward screening for compounds that decrease neurodegenerative diseases by administering a compound to a genetically altered Drosophila melanogaster fly that is predisposed to developing or has already developed symptoms of neurodegenerative disease in respect to i) a gene coding for HIF3a, ii) a

transcription product of a gene coding for HIF3a, iii) a translation product of a gene coding for HIF3a, and iv) a fragment, derivate or variant of i), ii) or iii). The specification and the art at the time of filing do not teach any neurodegenerative diseases that correlate to i) a gene coding for HIF3a, ii) a transcription product of a gene coding for HIF3a, iii) a translation product of a gene coding for HIF3a, and iv) a fragment, derivate or variant of i), ii) or iii). In particular, the specification and the art at the time of filing do not teach any genetically altered Drosophila melanogaster having a neurodegenerative disease that relates to i)-iv) as claimed. While Alzheimer's disease (AD) models were known in the art (pg 25, lines 15-24), the specification does not provide adequate guidance that known animal models of AD have "symptoms of neurodegenerative diseases or related diseases or disorders in respect of the substances recited in i)-iv)" as claimed, i.e. the specification does not teach the models correlate to wild-type, overexpression, deletion or mutation of HIF3a as encompassed by the claims. The specification does not provide any reason to believe that all models of AD correlate to HIF3a. Accordingly, it would have required those of skill undue experimentation to determine which "neurodegenerative diseases" in genetically altered Drosophila melanogaster are affected/caused by i) a gene coding for HIF3a, ii) a transcription product of a gene coding for HIF3a, iii) a translation product of a gene coding for HIF3a, and iv) a fragment, derivate or variant of i), ii) or iii) as broadly claimed.

The claims are directed toward screening for compounds that modulate neurodegenerative disease by

a) administering a compound to a genetically altered Drosophila melanogaster fly that is predisposed to developing or has already developed symptoms of neurodegenerative disease in respect to i) a gene coding for HIF3a, ii) a transcription product of a gene coding for HIF3a, iii) a translation product of a gene coding for HIF3a, and iv) a fragment, derivate or variant of i), ii) or iii);

b) measuring the activity and/or level of i) a gene coding for HIF3a, ii) a transcription product of a gene coding for HIF3a, iii) a translation product of a gene coding for HIF3a, and iv) a fragment, derivate or variant of i), ii) or iii);

c) measuring the activity and/or level of i)-iv) in a control Drosophila melanogaster fly that is predisposed to developing or has already developed symptoms of neurodegenerative disease in respect to i)-iv) to which no test compound has not been administered; and

d) comparing the activity and/or level of i)-iv) in the flies, wherein a change in the activity and/or level of i)-iv) indicates the test compound is a modulator of said neurodegenerative disease.

The specification states, “[t]o date, no experiments have been described that demonstrate a relationship between dysregulation of HIF3a gene expression and the pathology of neurodegenerative diseases, in particular AD [Alzheimer's Disease]. Likewise, no mutations in the HIF3a gene have been described to be associated with said diseases.” (pg 12, lines 1-6). Given the lack of guidance how to make or find such Drosophila melanogaster flies, it would require those of ordinary skill undue

experimentation to make Drosophila melanogaster flies with a genetic alteration in an HIF3a gene in the methods claimed.

Since the time of filing, Yamashita (Mol. Cell. Biol. Feb. 2008, Vol. 28, No. 4, pg 1285-1297) taught HIF3a knockout mice had enlarged right ventricles and impaired lung remodeling. The structure of the mice is encompassed by the structure of test animals in step a) of claim 11; the mice of Yamashita may fit the functional language in step a) as well because they may be predisposed to neurodegenerative disease. However, Yamashita did not teach they were a model of neurodegenerative disease. The specification does not teach HIF3a knockouts correlate to neurodegenerative disease. Therefore, the claims should not encompass using Drosophila with a knockout of HIF3a to screen for compounds that decrease neurodegenerative disease.

The specification describes making transgenic drosophila melanogaster expressing human BACE and HIF3a using the method of Greeve (pg 57, (xii)). The disclosure is not enabling because the specification taken with Greeve does not set for the structure of the construct used to make the files, that the transgenic flies had a neurodegenerative disease, or that the transgenic flies had a neurodegenerative disease that correlated to HIF3a overexpression in humans with neurodegenerative disease. The specification does not provide adequate guidance that the transgenic flies model neurodegenerative disease in humans. The specification teaches transgenic flies with HIF3a under the control of the eye specific gmr-GAL4 (pg 59, line 16). The specification does not teach how those flies model neurodegenerative disease as claimed. Without such guidance, it would have required those of skill undue

experimentation to determine how to make and use the transgenic flies described in the specification in the methods now claimed.

Claim 11 as newly amended encompasses using any Drosophila that is predisposed to developing or already developed symptoms of neurodegenerative disease. The claim is not limited to Drosophila overexpressing HIF3a or a variant thereof. The specification does not teach any genetically altered Drosophila that develop symptoms of neurodegenerative disease. While the specification teaches overexpressing hBACE and HIF3a in Drosophila (pg 57), the specification does not teach how to use any genetically altered Drosophila with any genetic alteration as broadly claimed including Drosophila expressing BACE and HIF3a to screen compounds that modulate HIF3a. The specification does not correlate the Drosophila on pg 57 to any other genetically altered Drosophila having neurodegenerative disease. Without such guidance, it would have required those of skill to use the Drosophila on pg 57 or any other genetically altered Drosophila having symptoms of neurodegeneration to screen compounds that modulate HIF3a to determine which decrease neurodegenerative disease.

The specification does not enable screening for modulators of SEQ ID NO: 4 (claim 26) using any Drosophila melanogaster fly predisposed to or having a neurodegenerative disease as claimed. The specification does not teach how to use any test animal having symptoms of Alzheimer's disease (AD), for example, to screen for modulators of SEQ ID NO: 4. Nor is such a method readily apparent from the art at the time of filing. If the test animal overexpresses amyloid precursor protein (APP) and

has symptoms of AD, for example, it cannot be determined how to use the mice to screen for modulators of SEQ ID NO: 4. Without such guidance, those of skill would be on their own to determine how to screen for modulators of SEQ ID NO: 4 using any test animal having symptoms of neurodegenerative disease, which is not considered an enabling disclosure.

Applicants argue Fig. 38 and pg 41 and 59-60 of parent application PCT/EP04/053573 (WO 2005/059562) disclosed a relationship between dysregulated HIF3a gene expression and the pathology of neurodegeneration. Applicants' argument is not persuasive. Pg 41 and Fig. 38 of '562 shows expression patterns of HIF3a in the brains of Alzheimer's patients at various stages. Figure 38 does not indicate overexpression of HIF3a causes Alzheimer's disease or that Drosophila that overexpress wild-type HIF3a are models of Alzheimer's disease. Furthermore, the Figure does not correlate to the vast number of genetically modified Drosophila encompassed by the claims. Pg 59-60 describes a transgenic fly co-expressing human amyloid precursor protein (hAPP), HIF3a sv3 and human BACE). The Drosophila contemplated in '562 does not correlate to the teachings in the specification originally filed. Pg 59-60 does not indicate overexpression of HIF3a alone or in combination with BACE and hAPP causes Alzheimer's disease or that Drosophila that overexpress wild-type HIF3a alone or in combination with BACE and hAPP are models of Alzheimer's disease. Furthermore, the Figure does not correlate to Drosophila having any of a vast number of genetic alterations that develop neurodegenerative disease encompassed by the claims. Accordingly, '562 fails to enable using the Drosophila disclosed by

applicants or any other genetic alteration as models of neurodegenerative disease or to screen compounds for treating neurodegenerative diseases as claimed.

Applicants point to pg 43, Fig. 42, of WO 2005/059562 for support of a phenotype correlating with symptoms of neurodegeneration. Applicants' argument is not persuasive. Fig. 42 relates to rescuing photoreceptor cell degeneration in flies expressing hAPP and hBACE. It is not clear photoreceptor cell degeneration is a symptom of neurodegeneration or that photoreceptor cell degeneration correlates to any and all symptoms of neurodegeneration claimed. The Fig. 42 does not correlate to screening compounds that modulate HIF3a as claimed. Drosophila expressing hAPP and hBACE do not correlate to Drosophila having any and all genetic alterations that develop neurodegenerative disease encompassed by the claims. More importantly, the Figure does not disclose how to use genetically altered Drosophila to screen compounds that modulate HIF3a.

Applicants argue those of skill would be able to make the "BACE fly model." It is presumed applicants refer to the Drosophila on pg 57 expressing human BACE and HIF3a. Applicants' argument is not persuasive. The disclosure is not enabling because the specification taken with Greeve does not set for the structure of the construct used to make the files. More importantly, the specification fails to teach how to use the flies by teaching the transgenic flies had a neurodegenerative disease, or that the transgenic flies had a neurodegenerative disease that correlated to HIF3a overexpression in humans with neurodegenerative disease. Furthermore, Drosophila expressing human

BACE and HIF3a does not correlate to the vast number of genetically altered Drosophila encompassed by the genetically altered Drosophila in claim 11.

If applicants have evidence that Drosophila expressing human BACE and HIF3a on pg 57 have symptoms of neurodegenerative disease, are models of Alzheimer's disease or model any other neurodegenerative disease, please provide such evidence specifically and point to the symptoms of neurodegeneration of such flies specifically. If applicants have evidence of any other Drosophila known in the art at the time of filing having symptoms of neurodegeneration that can be used to screen compounds that modulate HIF3a, please discuss such Drosophila specifically in the next response.

Indefiniteness

Claims 11, 12, 25 and 26 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claim 11 regarding the phrase "a test animal which is predisposed to developing or has already developed symptoms of a neurodegenerative disease or related diseases or disorders in respect of the substances selected from the group consisting of i) a gene coding for HIF3a, ii) a transcription product of a gene coding for HIF3a, iii) a translation product of a gene coding for HIF3a, and iv) a fragment, derivate or variant of i), ii) or iii)" has been withdrawn in view of the amendment.

The rejection regarding the metes and bounds of what applicants consider diseases "related" to neurodegenerative diseases (claim 11, preamble and step a)) has been withdrawn in view of the amendment.

The rejection regarding step c of claim 11 has been withdrawn.

Claim 11 as amended remains indefinite because it requires screening for a "compound that decreases neurodegenerative disease, wherein the compound is a modulator of one or more substances selected from the group consisting of i) a gene coding for HIF3a, ii) a transcription product of a gene coding for HIF3a, iii) a translation product of a gene coding for HIF3a, and iv) a fragment, derivate or variant of i), ii) or iii)." However, the body of the claim requires administering a test compound but does not require the test compound modulates HIF3a. Nor does the claim require determining which compounds modulate HIF3a. It is unclear how the compound in the preamble correlates to the test compound in the body of the claim. It appears the method may screen for modulators of HIF3a that decrease symptoms of neurodegenerative disease. If so, the steps for such screen should be clearly set forth, the preamble should be simplified and the body of the claim should have a step for determining compounds that modulate HIF3a AND decrease neurodegenerative disease.

Claim Rejections - 35 USC § 102

The rejection of claim 11 under 35 U.S.C. 102(a) as being anticipated by Heidbreder (FASEB, Aug. 2003, Vol. 17, pg 1541-1543) has been withdrawn because the claims are limited to using genetically altered Drosophila; Heidbreder related to using rats.

The rejection of claim 11 under 35 U.S.C. 102(a) as being anticipated by Makino (J. Biological Chem., Sept. 6, 2002, Vol. 277, No. 36, pg 32405-32408) has been withdrawn because the claims are limited to using genetically altered Drosophila while Makino is limited to using mice.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

/Michael C. Wilson/
Patent Examiner